IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :
SHIMIZU et al. :
Serial No. 10/017,755 : Group Art Unit 1615
Filed on October 30, 2001 : Examiner TRAN, Susan T
For RAPIDLY DISINTEGRABLE SOLID PREPARATION

DECLARATION UNDER 37 CFR §1.132

Honorable Commissioner of Patent and Trademarks, Washington, D.C.

Sir,

I, Toshihiro SHIMIZU, declare:

That I am a citizen of Japan residing at 15-3, Aramakiminami 2-chome, Itami-shi, Hyogo, Japan;

That I was born on July 10, 1964 in Okayama, Japan;

That I graduated from Gifu Pharmaceutical University, with degree of Bachelor of Pharmaceutical Science in March 1988;

That I have been employed by Takeda Chemical Industries, Ltd. (now, Takeda Pharmaceutical Company Limited), Osaka, Japan, since April, 1988, and have been engaged in research and development in the Pharmaceutical Production Division of said company;

That I have been appointed a Research Head of Pharmaceutical Technology Research & Development Laboratories in said Pharmaceutical Production Division since 2004;

That I was awarded a Ph. D in Formulation Study of Lansoprazole Fast-disintegrating Tablets containing Enteric Coated Microgranules from Kyushu University in March, 2005;

That I am a member of the Pharmaceutical Society of Japan, and have published, with other research workers, a number of reports on scientific studies, among others, including

1. Shimizu T., Nakano T., Morimoto S., Tabata T., Hamaguchi N., Igari Y., *Chem. Pharm. Bull.*, 51, 942-947 (2003)
2. Shimizu T., Kameoka N., Iki H., Tabata T., Hamaguchi N., Igari Y., *Chem. Pharm. Bull.*, 51, 1029-1035 (2003)
3. Shimizu T., Sugaya M., Nakano Y., Izutsu D., Mizukami Y., Okochi K., Tabata T., Hamaguchi N., Igari Y., *Chem. Pharm. Bull.*, 51, 1121-1127 (2003) ;

That I am one of the co-inventors of the United States Patent Application Serial No. 10/017,755 filed on October 30, 2001;

That the following Experiment was conducted by myself and under my supervision and control:

Study on Oral disintegrability of Effervescent Preparations by Lundberg *et al.*

PURPOSE

The oral disintegrability of effervescent preparations of U.S. Patent No. 6,132,770 (Lundberg *et al.*) have been evaluated and then have been examined whether this patent could be directed to an invention for the use as an orally disintegrating tablet.

PROCEDURES

The oral disintegrability of the effervescent preparations of Lundberg *et al.* have been evaluated by using the preparation procedures and the combination ratios as set forth in Example 3 of Lundberg *et al.*, except omeprazole was replaced with lansoprazole. Comparisons between Example 3 of Lundberg *et al.* and this formulation, and the preparation methods thereof are shown.

1. Preparation of Enteric-coated Granules

1.1 Active Compound Layer

Table 1 Formulation of Core and Active Compound Layer

Material	Example 3	Studied Product
Non-pareil core	10.0 kg(63.3%)	750 g(63.3%)
Magnesium omeprazole	5.0 kg(31.6%)	-
Lansoprazole	-	375 g(31.6%)
Hydroxypropyl methylcellulose	0.8 kg(5.1%)	60 g(5.1%)
Purified water	14.3 kg	1072.5 g
Total	15.8 kg	1185.0 g

Lansoprazole and hydroxypropyl methylcellulose were dissolved and suspended in purified water. Using a Wurster equipped fluidized-bed granulator, the non-pareil core was spray-coated with the suspension and was dried.

1.2. Intermediate Layer

Table 2 Formulation of Intermediate Layer

Material	Example 3	Studied Product
Core material with active compound layer	14.6 kg(77.7%)	1095.0 g(77.7%)
Hydroxypropyl cellulose	1.5 kg(8.0%)	112.5 g(8.0%)
Talc	2.5 kg(13.3%)	187.5 g(13.3%)
Magensium Stearate	0.2 kg(1.0%)	15 g(1.0%)
Purified water	29.2 kg	2190.0 g
Total	18.8 kg	1410.0 g

Hydroxypropyl cellulose, talc and magnesium stearate were dissolved and suspended in purified water. Using a Wurster equipped fluidized-bed granulator, the core material with the active compound layer was spray-coated with the suspension and was dried.

1.3. Enteric Layer

Table 3 Formulation of Enteric Layer

Material	Example 3	Studied Product
Active granules	250 g(54.9%)	500.0 g(54.9%)
Methacrylic acid copolymer(30% suspension)	458 g(30.2%)	916.0 g(30.2%)
Triethyl citrate	41 g(9.0%)	82.0 g(9.0%)
Titanium dioxide	19 g(4.2%)	38.0 g(4.2%)
Mono- and diglycerides	7 g(1.5%)	14.0 g(1.5%)
Polysorbate 80	0.7 g(0.2%)	1.4 g(0.2%)
Purified water	329 kg	658.0 g
Total	455.1 g	910.2 g

A methacrylic acid copolymer (30% suspension) was adjusted to pH of 4.0 with a 0.5 M aqueous sodium hydroxide solution. Thereafter all of the triethyl citrate was added. (Suspension A).
Polysorbate 80 was dissolved in a portion of purified water and was heated to 70°C, to which was added mono- and diglycerides. The mixture was dispersed with a disperser and then cooled to room temperature (Emulsion B). Thereafter, titanium dioxide was added and dispersed to a portion of purified water (Suspension C). Emulsion B, Suspension C and the remaining purified water were portionwise added to Suspension A. Using a Wurster equipped fluidized-bed granulator, the active granules were spray-coated with the suspension and dried.

2. Effervescent Granules

Table 4 Formulation of Effervescent Granules

Material	Example 3	Studied Product
Citric acid anhydrous	11.4 kg(56.7%)	570.0 g(56.7%)
Sodium bicarbonate	8.4 kg(41.8%)	420.0 g(41.8%)
Polyvinylpyrrolidone K-25	0.3kg(1.5%)	15.0 g(1.5%)
EtOH 99%(w/v)	0.8 kg	40.0 g
Purified water	0.3 kg	15.0 g
Total	20.1 kg	1060.0 g

Polyvinylpyrrolidone K-25 was dissolved in a mixed solution of ethanol and purified water. Citric acid anhydrous and sodium bicarbonate were mixed by using a

mortar, which was then added and compounded to the mixed solution. Then, the mixture was dried at 55°C using a lathe dryer and was granulated using 1000 μm of a standard sieve.

3. Pre-mix of Sodium Carbonate

Table 5 Formulation of Effervescent Granules

Material	Example 3	Studied Product
Sodium carbonate anhydrous	38 g(18.6%)	76.0 g(18.6%)
Sorbitol	160 g(78.5%)	320.0 g(78.5%)
Antifoam M	5.8 g(2.9%)	11.6 g(2.9%)
Total	203.8 g	407.6 g

Using a mortar, sodium carbonate anhydrous, sorbitol and an antifoam M were mixed.

4. Mixed Granules and Tablets

Table 6 Formulation of Mixed Granules

Material	Example 3	Studied Product
Effervescent granules	909 g(76.4%)	909.0 g(76.4%)
Pre-mix	204 g(17.1%)	204.0 g(17.1%)
Sodium sterylfumarate	7 g(0.6%)	7.0 g(0.6%)
Enteric coated microgranules	70 g(5.9%)	70.0 g(5.9%)
Total	1190 g	1190.0 g

Effervescent granules, the pre-mix, sodium sterylfumarate and the enteric coated microgranules were mixed and put into 50 bags. 2970m g of the mixed granules were weighed, and made into tablets using a universal testing machine UH-10A (Shimadzu) and using a flat pestle having an angle of 25 mmϕ under a tableting pressure of 20 KN/punch.

5. Characteristics of Tablets

Thickness, hardness and friability of the orally disintegrating tablets were measured.

Thickness: Thickness of 4 tablets were measured using a Dialgauge and were averaged.

Hardness: Hardness of 10 tablets were measured using a hardness tester (Toyama Company) and were averaged.

Oral Disintegration Time: Three individuals participated in this test. The participants brushed their teeth before the test and then took one tablet without swallowing the tablet. Thereafter, the disintegration time of the tablet was measured.

RESULTS

The results of the measurements are shown in Table 7, as it can be seen the thickness and hardness equivalent to those in Example 3 were obtained. For the oral disintegrability, it was hard to retain the tablet in the mouth due to the generation of carbonic acids, and thus the individuals vomited the tablet after 3 minutes. Even in such a case, it was shown that the tablet did not disintegrate even approximately by half. Thus, it was determined that the effervescent granules had difficulty of being applied as an orally disintegrating tablet.

Table 7 Results of Measurements

	Example 3 (Values as described in Lundberg *et al.*)	Studied Product
Thickness (Average)	4.3 mm	4.29 mm
Hardness (Average)	77 N	77.9 N
Oral Disintegration Time	-	Not disintegrated for 3 minutes Not tolerated due to the generation of carbonic acids, which caused the tablet to be vomited.

CONCLUSION

As described in European Pharmacopoeia, effervescent tablets are uncoated tablets generally containing acid substances and carbonates or hydrogen carbonates which react in the presence of water to release carbon dioxide. They are intended to be dissolved and dispersed in water before administration. On the other hand, orodispersible tablets (orally disintegrating tablets) are uncoated tablets intended to be placed in the mouth where they can disperse rapidly before being swallowed. Effervescent tablets and orally disintegrating tablets have different uses for taking a medicine. Therefore, we strongly believe that technologies for effervescent tablets don't apply to the design of orally disintegrating tablets.

The purpose of this study was to determine the possibility of application of technologies for effervescent tablets to the design of orally disintegrating tablets. The effervescent tablets of U.S. Patent No. 6,132,770 (Lundberg et al.) didn't disintegrate in the mouth within 3 minutes.

Therefore the above-described experiments confirm that technologies for effervescent tablets don't apply to the design of orally disintegrating tablets.

It is declared by the undersigned that all statements made herein of his knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 15th day of March, 2006.

Toshihiro Shimizu

Toshihiro SHIMIZU

For tablets for which subdivision is authorised, it is demonstrated to the satisfaction of the competent authority that the subdivided parts comply either with test A for *Uniformity of content of single-dose preparations* (*2.9.6*) or with the test for *Uniformity of mass of single-dose preparations* (*2.9.5*), as appropriate.

In the manufacture, packaging, storage and distribution of tablets, suitable means are taken to ensure their microbiological quality; recommendations on this aspect are provided in the text on *Microbiological quality of pharmaceutical preparations* (*5.1.4*).

TESTS

Uniformity of content (*2.9.6*). Unless otherwise prescribed or justified and authorised, tablets with a content of active substance less than 2 mg or less than 2 per cent of the total mass comply with test A for uniformity of content of single-dose preparations. If the preparation has more than one active substance, the requirement applies only to those substances which correspond to the above conditions.

Unless otherwise justified and authorised, coated tablets other than film-coated tablets comply with test A for uniformity of content of single-dose preparations irrespective of their content of active substance(s).

Uniformity of mass (*2.9.5*). Uncoated tablets and, unless otherwise justified and authorised, film-coated tablets comply with the test for uniformity of mass of single-dose preparations. If the test for uniformity of content is prescribed or justified and authorised for all the active substances, the test for uniformity of mass is not required.

Dissolution. A suitable test may be carried out to demonstrate the appropriate release of the active substance(s), for example one of the tests described in *Dissolution test for solid dosage forms* (*2.9.3*).

Where a dissolution test is prescribed, a disintegration test may not be required.

Uncoated tablets

DEFINITION

Uncoated tablets include single-layer tablets resulting from a single compression of particles and multi-layer tablets consisting of concentric or parallel layers obtained by successive compression of particles of different composition. The excipients used are not specifically intended to modify the release of the active substance in the digestive fluids.

Uncoated tablets conform to the general definition of tablets. A broken section, when examined under a lens, shows either a relatively uniform texture (single-layer tablets) or a stratified texture (multi-layer tablets) but no signs of coating.

TESTS

Disintegration. Uncoated tablets comply with the test for disintegration of tablets and capsules (*2.9.1*). Use *water R* as the liquid. Add a disc to each tube. Operate the apparatus for 15 min, unless otherwise justified and authorised, and examine the state of the tablets. If the tablets fail to comply because of adherence to the discs, repeat the test on a further 6 tablets omitting the discs. The tablets comply with the test if all 6 have disintegrated.

Chewable tablets are not required to comply with the test.

Coated tablets

DEFINITION

Coated tablets are tablets covered with one or more layers of mixtures of various substances such as natural or synthetic resins, gums, gelatin, inactive and insoluble fillers, sugars, plasticisers, polyols, waxes, colouring matter authorised by the competent authority and sometimes flavouring substances and active substances. The substances used as coatings are usually applied as a solution or suspension in conditions in which evaporation of the vehicle occurs. When the coating is a very thin polymeric coating, the tablets are known as film-coated tablets.

Coated tablets have a smooth surface which is often coloured and may be polished; a broken section, when examined under a lens, shows a core surrounded by one or more continuous layers with a different texture.

PRODUCTION

Where justified, uniformity of mass or uniformity of content of coated tablets other than film-coated tablets may be ensured by control of the cores.

TESTS

Disintegration. Coated tablets other than film-coated tablets comply with the test for disintegration of tablets and capsules (*2.9.1*). Use *water R* as the liquid. Add a disc to each tube. Operate the apparatus for 60 min, unless otherwise justified and authorised, and examine the state of the tablets. If any of the tablets has not disintegrated, repeat the test on a further 6 tablets, replacing *water R* with *0.1 M hydrochloric acid*. The tablets comply with the test if all 6 have disintegrated in the acid medium.

Film-coated tablets comply with the disintegration test prescribed above except that the apparatus is operated for 30 min, unless otherwise justified and authorised.

If coated tablets or film-coated tablets fail to comply because of adherence to the discs, repeat the test on a further 6 tablets omitting the discs. The tablets comply with the test if all 6 have disintegrated.

Chewable coated tablets are not required to comply with the test.

Effervescent tablets

DEFINITION

Effervescent tablets are uncoated tablets generally containing acid substances and carbonates or hydrogen carbonates which react rapidly in the presence of water to release carbon dioxide. They are intended to be dissolved or dispersed in water before administration.

TESTS

Disintegration. Place 1 tablet in a beaker containing 200 ml of *water R* at 15-25 °C; numerous bubbles of gas are evolved. When the evolution of gas around the tablet or its fragments ceases the tablet has disintegrated, being either dissolved or dispersed in the water so that no agglomerates of particles remain. Repeat the operation on 5 other tablets. The tablets comply with the test if each of the 6 tablets used disintegrates in the manner prescribed within 5 min, unless otherwise justified and authorised.

Soluble tablets

DEFINITION

Soluble tablets are uncoated or film-coated tablets. They are intended to be dissolved in water before administration. The solution produced may be slightly opalescent due to the added excipients used in the manufacture of the tablets.

TESTS

Disintegration. Soluble tablets disintegrate within 3 min when examined by the test for disintegration of tablets and capsules (*2.9.1*), but using *water R* at 15-25 °C.

Dispersible tablets

DEFINITION

Dispersible tablets are uncoated or film-coated tablets intended to be dispersed in water before administration giving a homogeneous dispersion.

TESTS

Disintegration. Dispersible tablets disintegrate within 3 min when examined by the test for disintegration of tablets and capsules (*2.9.1*), but using *water R* at 15-25 °C.

Fineness of dispersion. Place 2 tablets in 100 ml of *water R* and stir until completely dispersed. A smooth dispersion is produced, which passes through a sieve screen with a nominal mesh aperture of 710 µm.

Orodispersible tablets

DEFINITION

Orodispersible tablets are uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed.

TESTS

Disintegration. Orodispersible tablets disintegrate within 3 min when examined by the test for disintegration of tablets and capsules (*2.9.1*).

Modified-release tablets

DEFINITION

Modified-release tablets are coated or uncoated tablets which contain special excipients or which are prepared by special procedures, or both, designed to modify the rate, the place or the time at which the active substance(s) are released.

Modified-release tablets include prolonged-release tablets, delayed-release tablets and pulsatile-release tablets.

PRODUCTION

A suitable test is carried out to demonstrate the appropriate release of the active substance(s).

Gastro-resistant tablets

DEFINITION

Gastro-resistant tablets are delayed-release tablets that are intended to resist the gastric fluid and to release their active substance(s) in the intestinal fluid. Usually they are prepared from granules or particles already covered with a gastro-resistant coating or in certain cases by covering tablets with a gastro-resistant coating (enteric-coated tablets).

Tablets covered with a gastro-resistant coating conform to the definition of coated tablets.

PRODUCTION

For tablets prepared from granules or particles already covered with a gastro-resistant coating, a suitable test is carried out to demonstrate the appropriate release of the active substance(s).

TESTS

Disintegration. For tablets covered with a gastro-resistant coating carry out the test for disintegration (*2.9.1*) with the following modifications. Use *0.1 M hydrochloric acid* as the liquid. Operate the apparatus for 2 h, or other such time as may be justified and authorised, without the discs and examine the state of the tablets. The time of resistance to the acid medium varies according to the formulation of the tablets to be examined. It is typically 2 h to 3 h but even with authorised deviations is not less than 1 h. No tablet shows signs of either disintegration (apart from fragments of coating) or cracks that would allow the escape of the contents. Replace the acid by *phosphate buffer solution pH 6.8 R* and add a disc to each tube. Operate the apparatus for 60 min and examine the state of the tablets. If the tablets fail to comply because of adherence to the discs, repeat the test on a further 6 tablets omitting the discs. The tablets comply with the test if all 6 have disintegrated.

Dissolution. For tablets prepared from granules or particles already covered with a gastro-resistant coating, a suitable test is carried out to demonstrate the appropriate release of the active substance(s), for example the test described in *Dissolution test for solid dosage forms* (*2.9.3*).

Tablets for use in the mouth

DEFINITION

Tablets for use in the mouth are usually uncoated tablets. They are formulated to effect a slow release and local action of the active substance(s) or the release and absorption of the active substance or substances at a defined part of the mouth. They comply with the requirements of the monograph on *Oromucosal preparations (1807)*.

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TAMPONS, MEDICATED

Tamponae medicatae

Additional requirements for medicated tampons may be found, where appropriate, in other general monographs, for example Rectal preparations (1145), Vaginal preparations (1164) and Ear preparations (0652).

DEFINITION

Medicated tampons are solid, single-dose preparations intended to be inserted into the body cavities for a limited period of time. They consist of a suitable material such as cellulose, collagen or silicone impregnated with one or more active substances.

PRODUCTION

In the manufacture, packaging, storage and distribution of medicated tampons, suitable means are taken to ensure their microbial quality; recommendations on this aspect are provided in the text on *Microbiological quality of pharmaceutical preparations* (*5.1.4*).

LABELLING

The label states the quantity of active substance(s) per tampon.